UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,742	12/31/2003	Raymond P. Warrell JR.	12475/50502	1835

7590 02/06/2006

Kenyon & Kenyon
One Broadway
New York, NY 10004

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,742	WARRELL ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-152* is/are pending in the application.

4a) Of the above claim(s) *7,28-47 and 56-148* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-27,48-55 and 149-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on January 3, 2006 in response to the Restriction Requirement of November 1, 2005 has been entered. Applicant's election without traverse of Group I, claims 1-6, 9-16, 17-19, 20, 21-71, 149-150, as specifically drawn to a therapeutic regimen for a mammal with a neoplastic disease, comprising the steps of administering a therapeutic dose of a gallium compound and administering a therapeutic dose of an antibody has been acknowledged. As requested by Applicants, Claim 8 will be included in the election of Group I. Because applicants elected without traverse, the restriction requirement is therefore deemed to be proper and is made FINAL.

Species Election

Applicant's election of the species Rituximab from Claim 20 is acknowledged and has been entered.

Claims 1-152 are currently pending.

Claims 7 and 72-148 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 28-47 and 56-71 are withdrawn from prosecution on the merits as being drawn to non-elected species.

Claims 1-6, 8-27, 48-55 and 149-152 are currently under consideration for prosecution on the merits.

Specification

The disclosure is objected to because of the following informalities:

The specification on page 1 should be amended to reflect the priority status of the present application, for example: The present application is a non-provisional application with

which claims the benefit of priority of United States Provisional Application Serial No. 60/473,275 filed on 12/31/2002, now abandoned, the entire contents of which are incorporated herein by reference.

Moreover, the specification, as originally filed, does not appear to have any page numbers.

Appropriate correction is required.

Claim Objections

Claims 1 and 8-9 are objected to because of the following informalities:

Claim 1 is objected to for the recitation of "a treatment regimen". While on the dependent claims thereof refer to claim 1 as a method, the terminology is still confusing. For clarity, the Examiner suggests that Claim 1 be amended to recite "A method of treating a mammal with a neoplastic disease....".

Claim 8 recites non-elected subject matter, i.e. Claim 7.

Claims 9 recites non-elected subject matter such as an antisense molecule, an anti-telomerase agent, a biologic modifier... an arsenic compound.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-6, 9-10, 17-27 and 149-152 are rejected under 35 U.S.C. 102(b) as being anticipated by Grillo-Lopez, A. (WO 01/80884, 11/1/2001).

Grillo-Lopez teaches (page 68, lines 3-4 and page 73, lines 5-6, 29) a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an ant-CD20 antibody or fragment thereof in combination with gallium nitrate.

With regards to a CNS lymphoma, the WO document teaches (page 10, lines 24-27) that CNS lymphoma include, but are not limited to, Hodgkin's Disease lymphomas, non-Hodgkin's lymphoma (NHL), leptomeningeal metastasis and primary CNS lymphoma (PCNSL). With regards to the antibody, the WO document teaches (page 9, lines 26-28) that the anti-CD20 antibodies include, but are not limited to, human antibodies, humanized antibodies, bispecific antibodies and chimeric antibodies. Specifically, Grillo-Lopez teaches (page 20, line 30 to page 21, line 6) that the preferred anti-CD20 antibody is rituximab. With regards to the dose of the antibody, the WO document teaches (page 10, line 1-4) that the typical dose ranges from about 10 to about 375 mg/m^2 per week for 4 weeks. Thus, while Grillo-Lopez does not explicitly characterize the CNS lymphoma's as a neoplastic disease, the claim language or limitation does appear to result in a manipulative difference between the prior art and the instantly claimed method since the specification discusses (page 7, lines 13-31) that neoplasm includes, but is not limited to, hematologic malignancies such as Non-Hodgkin's lymphoma. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grillo-Lopez, A (WO 01/80884, 11/2/2001).

Grillo-Lopez teaches, as applied to claims 1, 6, 9-10, 17-27 and 149-152 above, a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an ant-CD20 antibody or fragment thereof in combination with gallium nitrate (page 68, lines 3-4 and page 73, lines 5-6, 29). With regards to a CNS lymphoma, the WO document teaches (page 10, lines 24-27) that CNS lymphoma include, but are not limited to Hodkins Disease lymphomas, non-Hodkin's lymphoma (NHL), leptomeningeal metastasis and

primary CNS lymphoma (PCNSL). With regards to the antibody, the WO document teaches (page 9, lines 26-28) that the anti-CD20 antibodies include, but are not limited to, human antibodies, humanized antibodies, bispecific antibodies and chimeric antibodies. Specifically, Grillo-Lopez teaches (page 20, line 30 to page 21, line 6) that the preferred anti-CD20 antibody is rituximab. With regards to the dose of the antibody, the WO document teaches (page 10, line 1-4) that the typical dosage ranges from about 10 to about 375 mg/m^2 per week for 4 weeks.
Grillo-Lopez does not explicitly teach that the gallium nitrate and Rituximab are administered simultaneously or separately, where in the separate administration occurs at selected time interval.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the administration schedule and time interval of gallium nitrate and the antibody. One would have been motivated to do so because where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. As such, one would have a reasonable expectation of success that by optimizing the administration schedule, one would achieve a successful method of treating cancer.

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grillo-Lopez, A (WO 01/80884, 11/2/2001) in further view of Warrell et al. (Cancer 1983; 51: 1982-1987).

Grillo-Lopez teaches, as applied to claims 1-6, 9-10, 17-27 and 149-152 above, a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an ant-CD20 antibody or fragment thereof in combination with gallium nitrate (page 68, lines 3-4 and page 73, lines 5-6, 29). With regards to a CNS lymphoma, the WO document teaches (page 10, lines 24-27) that CNS lymphoma include, but are not limited to Hodkins Disease lymphomas, non-Hodkin's lymphoma (NHL), leptomeningeal metastasis and primary CNS lymphoma (PCNSL). With regards to the antibody, the WO document teaches (page 9, lines 26-28) that the anti-CD20 antibodies include, but are not limited to, human antibodies, humanized antibodies, bispecific antibodies and chimeric antibodies. Specifically, Grillo-Lopez teaches (page 20, line 30 to page 21, line 6) that the preferred anti-CD20 antibody is rituximab. With regards to the dose of the antibody, the WO document teaches (page 10, line 1-4) that the typical dosage ranges from about 10 to about 375 mg/m^2 per week for 4 weeks.

Grillo-Lopez does not explicitly teach that the dose of gallium nitrate is about 100 to about 400 mg/m2/day, 250 to about 350 mg/m2/day, or 300 mg/m2/day. Nor does Grillo-Lopez teach that gallium nitrate is administered over about 3 days to about 8 days, about 5 days to about 7 days or about 7 days.

Warrell et al. teach the treatment of patients with advanced malignant lymphoma using gallium nitrate administered as a seven day continuous infusion. Specifically, the reference teaches that gallium nitrate administered as a continuous infusion for seven days at 300mg/m2/day is a well tolerated and effective treatment of patients with advanced malignant lymphoma (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of treating a lymphoma comprising administering a therapeutically effective amount of Rituximab in combination with gallium nitrate as taught by Grillo-Lopez with the dosing and administration schedule as taught by Warrell et al.. One would have been motivated to do so because as evidenced by Warrell et al., continuous infusion for seven days of 300mg/m2/day of gallium nitrate is an effective treatment of patients with advanced malignant lymphoma (abstract). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using a continuous seven day infusion of 300 mg/m2/day gallium nitrate in the method taught by Grillo-Lopex in view of Warrell et al., one would achieve an effective method of treating a CNS lymphoma.

Claims 48-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Grillo-Lopez, A (WO 01/80884, 11/2/2001) and Warrell et al. (Cancer 1983; 51: 1982-1987) in further view of Zevalin (Package Insert, 12/21/2001) (referred to herein as "The Zevalin Package Insert).

The combination of Grillo-Lopez and Warrell et al. teach, as applied to claims 1-6, 9-27 and 149-152 above, a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an ant-CD20 antibody or fragment thereof in combination with gallium nitrate (page 68, lines 3-4 and page 73, lines 5-6, 29). Specifically, Grillo-Lopez teaches (page 20, line 30 to page 21, line 6) that the preferred anti-CD20 antibody is rituximab, wherein the typical dose ranges about 10 to about 375 mg/m^2 per week for 4 weeks. Warrell et al. teach the effective dose and administration protocol for gallium nitrate treatment of malignant lymphomas.

Warrell et al. teach the treatment of patients with advanced malignant lymphoma using gallium nitrate administered as a seven day continuous infusion. Specifically, the reference teaches that gallium nitrate administered as a continuous infusion for seven days at 300mg/m2/day is a well-tolerated and effective treatment of patients with advanced malignant lymphoma (abstract).

The combination of Grillo-Lopez and Warrell et al. does not explicitly teach that the administration of a first antibody and a second antibody, wherein the first antibody is rituximab and the second antibody is ibritumomab tiuxetan. Nor does the combination teach the initial dose or second dose of either rituximab or ibritumomab tiuxetan.

The Zevalin Package Insert teaches that Zevalin, also referred to as Ibritumomab Tiuxetan, is an immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody Ibritumomab and the linker-chelator tiuxetan (page 2 of 38). The Zevalin Package Insert further teaches (page 22 or 38 and page 11 of 38) that a Zevalin therapeutic regimen is used for the treatment of patient with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma including patients with Rituximab refractory follicular non-Hodgkin's lymphoma, wherein the Zevalin treatment regimen consists of two steps: Step 1 includes a single infusion of 250 mg/m2 Rituximab preceding a fixed dose of 5.0 mCi of In-111 Zevalin administered as a 10 min IV push. Step 2 follows Step 1 by seven to nine days and consists of a second infusion of 250 mg/m2 of Rituximab prior to 0.4 mCi/kg or Y-90 Zevalin administered as a 10 minute push.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of treating a lymphoma comprising administering a therapeutically effective amount of Rituximab in combination with gallium nitrate as taught by Grillo-Lopez and Warrell et al. with a Zevalin therapeutic regimen instead of Rituximab alone in view of The Zevalin Package Insert. One would have been motivated to do so because as evidenced by The Zevalin Package Insert, the Zevalin therapeutic regimen is used for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma including patients with Rituximab refractory follicular non-Hodgkin's lymphoma (page 11 or 38). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method as taught by Grillo-Lopex and Warrell et al. to include the Zevalin therapeutic regimen instead of Rituximab alone, one would achieve an effective method of treating Rituximab refractory non-Hodgkin's lymphoma.

Therefore, NO claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Grillo-Lopez (US 2002/0009444, 1/24/2002)

Grewal (US 2002/0197256 A1, 12/26/2002)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
1/30/06